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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,727	09/30/2003	Alan Verkman	UCSF-291	2946

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EXAMINER	
SPIVACK, PHYLLIS G	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,727	VERKMAN ET AL.	
	Examiner	Art Unit	
	Phyllis G. Spivack	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *20-40 and 61-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 41-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A Response filed November 18, 2005 to a Restriction Requirement is acknowledged. Applicants have elected Group I, claims 1-19 and 41-60.

It is unclear whether or not claims 20-40 and 61-64 are intended to be canceled at this time. Clarification is requested.

Claims 20-40 and 61-64 are withdrawn from consideration by the Examiner, 37 CFR 1.142(b), as drawn to non-elected inventions. Accordingly, the subject matter presently under consideration are those methods of treating a cystic fibrosis transmembrane conductance regulator (CFTR) protein-mediated condition or symptom, treating a condition associated with aberrant ion transport by cystic fibrosis transmembrane conductance regulator (CFTR) and pharmaceutical compositions of instant formula I, claims 1-19 and 41-60. Re-affirmation of the election is requested when Applicants respond to this Office Action.

A Preliminary Amendment filed January 20, 2004 is further acknowledged. Updated priority information is noted.

The abstract of the disclosure is objected to because it is not directed to the subject matter presently under consideration. Correction is required. See MPEP § 608.01(b).

Claims 1-19 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. The claims are directed to treating a cystic fibrosis transmembrane conductance regulator (CFTR) protein-mediated condition or symptom

and treating any condition associated with aberrant ion transport by cystic fibrosis transmembrane conductance regulator (CFTR) comprising administering a compound of instant formula I or a thiazolidinone compound. The specification provides support for reducing intestinal fluid secretion in laboratory assays involving toxin-treated intestinal loops and in rat intestinal loops comprising administering a single compound, 3-[(3-trifluormethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone, referred to as $CFTR_{inh}$-172. The compound shows favorable antidiarrheal applications and prevents cAMP and cGMP induced ion/fluid secretion.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to treating a cystic fibrosis transmembrane conductance regulator (CFTR) protein-mediated condition or symptom and treating any condition associated with aberrant ion transport by cystic fibrosis transmembrane conductance regulator (CFTR) comprising administering a compound of instant formula I or a thiazolidinone compound. Given their broadest interpretation, the claims are drawn to methods of treating various pathologies, symptoms and conditions involved with the CFTR protein.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the area of CFTR protein chemistry.

Each particular type of pathology, symptom and condition involved with the CFTR protein would reasonably have its own specific characteristics and etiology. The broad recitations "treating a subject having a cystic fibrosis transmembrane conductance regulator (CFTR) protein-mediated condition or symptom" and treating any "condition associated with aberrant ion transport by cystic fibrosis transmembrane conductance regulator (CFTR) in a subject" comprising administering a compound of instant formula I or a thiazolidinone compound are inclusive of many conditions that presently have no established successful therapies. A successful treatment modality for one particular type of pathology, symptom or condition involved with the CFTR protein does not presage success for treating another type.

The breadth of the claims

The claims are very broad and inclusive of any condition associated with aberrant ion transport cystic fibrosis transmembrane conductance regulator (CFTR) in a subject and any condition or symptom involved with the CFTR protein.

The amount of direction or guidance provided and the presence or absence of working examples

All working examples are limited to the administration of a single compound, 3-[(3-trifluormethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone, referred to as $CFTR_{inh}$-172. No guidance is provided to select another of the plethora of compounds encompassed in the depiction of instant formula I. The subject matter encompassed in the language of instant claims 1 and 41 are clearly beyond the scope of the instant disclosure.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular compound would be preferred for treating the various conditions and symptoms associated with the CFTR protein or aberrant ion transport by CFTR that are broadly encompassed in the claim language. Those disease states contemplated are absent. The skilled artisan would expect the interaction of a particular compound in the treatment of a particular type of CFTR protein pathology, or aberrant ion transport by CFTR, to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding. No direction is provided to distinguish both therapy among the various types of pathologies

encompassed in the claim language and the preferred compounds for a specific therapeutic outcome. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic agent to treat any particular type of condition or symptom involving the CFTR protein or aberrant ion transport by CFTR, one skilled in the art would have to test extensively many compounds of instant formula I to discover which particular type of condition or symptom involving the CFTR protein or aberrant ion transport by CFTR responds to a particular compound. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Considering the state of the art as disclosed by the prior art of record, the high unpredictability of treating any condition or symptom involving the CFTR protein or aberrant ion transport by CFTR, and the lack of guidance provided by the specification, one of ordinary skill in the art would be burdened with undue experimentation to treat all conditions and symptoms comprising administering any of the numerous compounds of instant formula I.

Claims 1-19 and 46-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and under 35 U.S.C. 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, Applicant must convey with reasonable clarity, as of the filing date, that Applicant was in possession of the claimed invention. The issue of a lack of adequate written description also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996), (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that Applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. For example, a specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the

claims and determined that the invention would work for its intended purpose. An Applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that Applicant was in possession of the claimed invention as a whole.

An Applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics that provide evidence that Applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if

the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

Applicants have not conveyed possession of the invention with reasonable clarity to one skilled in the art. There are no working examples directed to administration of a compound of instant formula I wherein selenium is employed for either the A_3 or A_4 terms. Further, the metes and bounds of "an organic group", "an electron-withdrawing group" and the recitations "A_4 comprises one or more carbons or heteroatoms and may be present or absent" and "a pharmaceutically acceptable derivative" cannot be precisely determined. In view of the various functionalities encompassed in the language of the claims, steric hindrance and receptor selectivity, the skilled artisan would reasonably require a more detailed description of those compounds contemplated. Applicants have not provided any working examples that would describe to one of ordinary skill in the art an embodiment that meets all the limitations thereof. Applicants have not described with sufficient clarity pharmaceutical compositions wherein such compounds having of "an organic group", wherein "A_4 comprises one or more carbons or heteroatoms and may be present or absent" and "a pharmaceutically acceptable derivative" have been prepared. Sufficient guidance to support predictable operability of the invention to one of ordinary skill in the art is absent.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 46-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Roman et al., Farmatsevtichnii Zhurnal (abstract).

Roman teaches the preparation of compounds for therapeutic application comprising 3-aryl-5-arylidene-2-thioxothiazolidine-4-ones of instant formula I. Applicants are not entitled to procure claims based on discovery that known compositions of matter can be adapted to a new use. Merely reciting the intended use of an old composition does not impart patentability thereto. *In re Hack*, 114 USPQ 161. See MPEP 2112.01.

No claim is allowed.

Ma et al., J. Biol. Chem., and Ma et al., The Journal of Clinical Investigation, are cited to show further the state of the art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached from 10:30 to 7 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached 571-272-951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis Spivack

February 20, 2006 Phyllis Spivack

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PRIMARY EXAMINER